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E D I T O R I A L

DRUG OR BEVERAGE?

WHILE we have the highest regard for aspirin as a drug and believe it to be one of the most useful of all household remedies, we must take exception to the efforts of one of our major drug companies to promote its sale. They are planning again this summer to build sales volume using the slogan, "Take a Bayer Break." The theme, according to their press release, is "When You're Feeling 'Heat-Beat' (Tense, Irritable, Headachy) . . . Take a Bayer Break."

Promotional efforts such as this are largely responsible for the attitude which is developing among the laity to consider the habitual use of a drug a perfectly normal procedure and one not likely to do any harm whatsoever. From such advertising, one would almost gain the impression that aspirin is in the same category as are basic nutrients, beverages, and such accessory food substances as the vitamins. The fact that aspirin, like all drugs, is entirely foreign to the human body and can in some instances do great damage is completely obscured by such high pressure advertising.

It is difficult to reconcile such blatant promotional efforts with the failure of the health professions including pharmacy to register their strong disapproval of this program and, insofar as pharmacists are concerned, refuse to be a party to it. We have no quarrel with the use of home remedies by the layman providing his need is clear-cut and providing, furthermore, that someone with some professional competence has used some judgment concerning this need. We are strongly opposed to the philosophy which is developing in this country that drugs are simply ordinary commodities like all other things offered for sale to the public to be advertised and sold with all of the skill and adroitness that the Madison Avenue boys can conjure up. It is, after all, entirely possible that some few people can manage to go through life without dosing themselves regularly with aspirin in order to feel perfectly normal and well, and it is equally possible that

many persons may be doing themselves irreparable harm by the all-too-simple purchase and use of this "wonder drug." If indeed aspirin were totally without toxicity—which all of us know it is not—it still could cause great harm if only by leading the unsuspecting person to postpone for too long proper diagnosis and treatment. It would be an interesting thing to know how many people do this very thing each year for such is the risk when palliatives are used, whatever their nature. It is also an established fact that analgesics such as aspirin are likely to cause a psychological dependence in many people with resulting habituation.

For a long time now, we have seen the public exploited by creating in their minds the concept that many things which are basically harmful are entirely safe and almost necessary if one wishes to be well, happy, and socially acceptable. For example, the promotional efforts used in building sales volume for cigarettes and alcoholic beverages are nothing short of a national disgrace. It hurts us as members of a health profession to see drugs being promoted by the same techniques, and it hurts even worse to see our professional brethren cooperate in these efforts.

L. F. Tice

PSYCHOTHERAPEUTIC DRUGS

By G. Victor Rossi *

PERHAPS one of the most significant medical advances of the past decade has been the breathing of new life into the time-honored concept of "a sound mind in a sound body". Thus, in a decade when man literally reached for the stars, we have witnessed the rebirth of a medical perspective whose long-range implications may be more significant than our spectacular astrophysical accomplishments. This rebirth has been catalyzed by the introduction and enthusiastic acceptance of PSYCHOTHERAPEUTIC DRUGS—a diverse group of naturally-occurring and synthetic chemical substances employed in the therapy of mental illness. The challenging need for effective approaches to the treatment of mental and emotional disorders is emphasized by the title of Gorman's book, *Every Other Bed* (1), which alludes to the fact that about half of the hospital beds in the nation are occupied by mental patients. Psychotherapeutic drugs have provided a two-fold answer to this challenge. Their immediate practical value in alleviating the symptoms of mental aberrations, albeit without effecting cures, is well documented. More importantly, psychotherapeutic agents have provided the impetus for attempts to "unravel the tangled skein of abnormal behavior".

Since the dawn of time, man has displayed a marvelous ingenuity for discovering drugs which affect the central nervous system in his ageless quest for "peace of mind". Hashish, cocaine, opium, and alcohol have all served as a magic carpet for the "flight from reality". Although certain of the pharmacologic properties of these substances might be embodied in clinically useful psychotherapeutic agents, their over-all spectrum of activity precludes their widespread use in the therapy of mental illness. They produce such generalized impairment of sensory and motor function as to seriously interfere with routine activity. This latter deterrent is shared by chloral, the bromides,

* Department of Pharmacology, Philadelphia College of Pharmacy and Science, Philadelphia 4, Pa. Presented at the Seminar on Tranquilizing Drugs sponsored by the Kentucky Academy of General Practice, Cincinnati, Ohio, January 21, 1960.

the barbiturates, and many other sedative-hypnotic drugs. The last decade has spawned a new order of drugs which represent a dramatic departure from previously employed approaches to the therapy of behavioral disturbances. These drugs may benefit mental and emotional disorders without significantly altering consciousness or body function—a highly desirable goal in the therapeutic process. The *ataraxics* or tranquilizers appear to reduce tension, apprehension, anxiety, and other symptoms of certain psychiatric illnesses. The more recently introduced *psychic energizers* have a diverse effect in that they appear to increase the vigor of psychological functioning and to ameliorate certain forms of depression.

Sites and Mechanisms of Action

Himwich (2) states that barbiturates act largely on the cerebral cortex, thereby depressing functions of the cortical regions concerned with the analyzing mechanisms of vision, audition, and other perceptive functions—the fine coordination of motor movements as well as thought and memory. Although the ataraxics, as a group, also affect functions ascribed to the cerebral cortex, they exert their actions principally on the subcortical structures considered as comprising the "anatomic substrate of emotion"—the midbrain reticular formation, the hypothalamus, and components of the rhinencephalon. Bradley (3, 4) also considers that the actions of the ataraxics may be ascribed to their effects on the reticular formation and the thalamic projection system or alteration of afferent input to the reticular system. When used in amounts sufficient to calm the disturbed psychiatric patient, the barbiturates leave a wake of drowsiness, dizziness, ataxia, or hypnosis, which seldom lightens the custodial problem. Possibly as a reflection of their contrasting sites of action, the ataraxics reduce anxiety, tension, agitation, or disturbed behavior without marked degrees of sedation or sleepiness. Achievement of the desired therapeutic response without dulling the senses, without decreasing perception or interfering with mental acuity is indeed a desirable goal, frequently attainable by critical selection and judicious use of ataractic agents.

Brodie (5) has offered an interpretation of the mechanism of action of psychotropic drugs based largely on the physiologic concepts of Hess (6), who postulated that reactions to environmental changes are controlled by a subcortical system integrating autonomic, somatic,

and psychic functions. Hess proposed that the subcortical system, like the peripheral autonomic nervous system, consists of two mutually antagonistic divisions. The *trophotropic* division is considered to integrate parasympathetic with somatomotor activities to produce behavioral patterns that conserve and restore energy. Trophotropic predominance is associated with sedation, increased parasympathetic activity, decreased skeletal muscle tone, and decreased reactivity to sensory stimuli. The *ergotropic* division is depicted as integrating sympathetic with somatomotor activities to produce patterns of behavior which prepare the body for positive action. Ergotropic predominance, in contrast, is correlated with arousal, increased sympathetic activity, enhanced skeletal muscle tone and activity, and an activated psychic state. There is considerable, if not altogether conclusive, evidence that *serotonin* (5-hydroxytryptamine) serves as the chemical mediator of nerve impulse transmission in the trophotropic division, and that *norepinephrine* functions as the neurohormone of the ergotropic division. Following the release of these biogenic amines in their free (active) form, as a result of nerve impulses or the presence of centrally-acting drugs, their inactivation is catalyzed by the enzyme *monoamine oxidase*.

Certain tranquilizing drugs may influence behavior by shifting the balance of the opposing diencephalic systems toward trophotropic predominance. The trophotropic syndrome elicited by reserpine and the related rauwolfia alkaloids, deserpidine and rescinnamine, has been considered a result of their action which releases free serotonin in the brain (*7*). Chlorpromazine and its many analogs produce symptoms of trophotropic predominance, apparently by blocking the action of brain norepinephrine and thus inhibiting the ergotropic division. It has been suggested that the term central adrenergic blocking agent may be used to describe the central actions of the phenothiazine ataraxics.

Certain central stimulants may affect behavior by shifting the balance of opposing subcortical activities toward ergotropic predominance. Adrenergic agents such as the amphetamines, ephedrine, and desoxyephedrine are phenylethylamine analogs of the neurohormone, norepinephrine. These drugs may be considered to mimic the action of norepinephrine at ergotropic receptor sites, thereby inducing arousal, increased central sympathetic outflow, increased psychomotor activity, and enhanced sensitivity to external stimuli. The efficacy

of these adrenergic amines as antidepressants is somewhat compromised by their activity at peripheral sympathetic sites, which may lead to undesirable cardiovascular responses. In contrast, the phenylethylamines, methylphenidate (RITALIN®) and pipradol (MERATRAN®), may be classified as central adrenergic agents which exert only minimal direct action on the peripheral sympathetic system. The antidepressant drugs, categorized as *amine oxidase inhibitors,* also cause ergotropic predominance, possibly as a result of an increase in the level of norepinephrine in the brain.

The proposals briefly outlined in the foregoing may represent interpretations of biochemical and functional changes produced by certain drugs which are specifically, or perhaps only coincidentally, related to the mechanisms by which they exert their characteristic psychotherapeutic effects. Schneider and Sigg (8) conclude that these drugs influence functions of the central nervous system which as yet have not been successfully studied experimentally. Baker (9) has aptly stated that our knowledge of the action of drugs on the central nervous system is incomplete and that the practical applications of psychotropic drugs are surpassing any theoretical basis for their action. We might note that it is now more than a century since the discovery of anesthetics "changed the operating room from a chamber of horrors to a place where the tranquility of unconsciousness supervenes" (10). Although we still do not have an acceptable theory of anesthesia, the progress in this field over the past century has been phenomenal.

There are three major groups of artaraxics or tranquilizing drugs—the phenothiazine derivatives, the rauwolfia alkaloids, and a chemically heterogeneous group of neurosedatives.

Phenothiazine Derivatives

Phenothiazine, the parent structure of a large group of ataraxics, has long been recognized as an effective but highly toxic anthelmintic. Chlorpromazine was discovered in 1951 at the Rhone-Poulenc Specia Research Laboratories in France during an intensive search for new, clinically useful phenothiazine derivatives. In 1952, Laborit and his associates (11) reported the results of studies with their "lytic cocktail", a major component of which was chlorpromazine. The immediate acceptance and subsequent widespread use of chlorproma-

zine fostered the development of a host of related molecules. There are currently sixteen members of this series in use and many others undergoing experimental study or clinical evaluation. Although the same structural nucleus is common to each of these ataraxics, they differ in the nature of ring and side-chain substitutions, which is reflected in variations in potency, specificity of action, and the frequency with which certain types of side-effects and toxic reactions occur. Selection of the agent which will provide the maximum therapeutic response coincident with a minimum of untoward reactions remains largely an empirical matter. With the advent of each new contender in the psychotherapeutic field, the decision as to the best among them becomes more perplexing. However, the physician has always been faced with the task of balancing the therapeutic value of each drug he prescribes against the potential hazards involved in its use. The ability to arrive at a proper decision represents a part of the successful practice of medicine (12).

Although there is still an inadequate basis for a definitive classification of the phenothiazines, an attempt to group them in broad categories may be helpful (see Appendix). The very potent, generally more toxic members of this series which are primarily indicated in the treatment of severe psychotic states and extreme agitation, include chlorpromazine (THORAZINE®), trifluoperazine (STELAZINE®), and trifluprom azine (VESPRIN®). Among the highly effective tranquilizers which are useful in mild psychoneurotic agitation, anxiety, fear, and tension, as well as in more severe psychotic disturbances, may be included fluphenazine (PERMITIL® or PROLIXIN®), perphenazine (TRILAFON®), prochlorperazine (COMPAZINE®), and thiopropazate (DARTAL®).

Phenothiazine tranquilizers which are less potent, somewhat less toxic, generally not as effective in the control of severe psychotic states, extreme agitation, nausea and vomiting, but which may be adequate in the treatment of milder mental or emotional disturbances, include acepromazine (PLEGICIL®), mepazine (PACATAL®), methoxypromazine (TENTONE®), promazine (SPARINE®), promethazine (PHENERGAN®), and thioridazine (MELLARIL®).

Two phenothiazines which have selective utility are thioperazine (VONTIL®), perhaps the most powerful antiemetic available, and trimeprazine (TEMARIL®), a highly effective antipruritic. Both of these agents have limited tranquilizing activity.

Several years of experience with chlorpromazine and related phenothiazines has taught us what side-effects frequently, and toxic reaction occasionally, may be expected to result from the administration of these ataraxics. Undesirable effects which occur in many patients and which often appear to be related to the amount of drug administered, include drowsiness, hypotonia with weakness and fatigue, blurred vision, xerostomia, nausea and vomiting, postural hypotension, dermatitis, and extrapyramidal motor activity simulating Parkinson's disease.

It has been suggested that the Parkinsonian-like symptoms may be a consequence of an action on the ascending reticular activating system, since it has been shown that the brain-stem reticular formation plays a role in the genesis of the extrapyramidal symptoms of Parkinsonism (13). On the basis of data presently available, perphenazine, prochlorperazine, thiopropazate, and trifluperazine appear to cause more frequent and severe extrapyramidal symptoms than the other phenothiazines (14). Children are especially prone to the extrapyramidal effects of the phenothiazines. Concomitant administration of anti-Parkinsonism agents may relieve drug-induced tremors in those cases in which large doses of a phenothiazine are necessary to control severe psychotic symptoms. Thioridazine appears to be unique in that no extrapyramidal symptoms have thus far been observed from its use (14).

Toxic effects such as jaundice and agranulocytosis, which may be manifestations of special sensitivity reactions, occur in only a small percentage of persons treated with certain phenothiazines. The incidence of chlorpromazine-induced jaundice has been estimated to range from 0.8% with a low dosage for several weeks to 1.4% with a high dosage for many months (15). Symptoms of liver involvement have been observed during therapy with several phenothiazines, but the incidence is probably less than that reported for chlorpromazine. Phenothiazine-induced jaundice is generally self-limited, but permanent liver damage may result if administration of the drug is continued.

Agranulocytosis, although rare, has been reported to occur with chlorpromazine, mepazine, promazine, prochlorperazine, triflupromazine, and trimeprazine. The advisability of adequate hematological safeguards during treatment with the phenothiazine derivatives, including periodic leucocyte counts, has been recently emphasized (15).

Claims that the newer phenothiazine derivatives are less likely to cause serious blood dyscrasias may be somewhat premature.

Rauwolfia Alkaloids

The story of the Indian plant, Rauwolfia, is now classic. In this cosmopolitan age where the evidences of man's genius abound, the discovery of reserpine and related alkaloids should serve to remind us of nature's relatively untapped wealth of potent drugs. The powdered whole root of Rauwolfia serpentina and the alkaloidal fraction, termed alseroxylon, are employed primarily for their antihypertensive activity. Three Rauwolfia alkaloids, reserpine, deserpidine, and rescinnamine, have proven effective in controlling hyperactive, disturbed behavior in pyschiatric patients. The pharmacologic activity, potency, and clinical usefulness of all three alkaloids appear comparable. Side-effects associated with the use of deserpidine and rescinnamine, while qualitatively similar to those of reserpine, may be somewhat less frequent and less severe. These alkaloids are characterized by a spectrum of pharmacologic effects which include tranquilization, hypotension, bradycardia, myosis, ptosis, drop in body temperature, increased gastrointestinal motility and hypersecretion, and diarrhea.

The sedative action of reserpine has been attributed to interference with the storage of the biogenic amines, serotonin or norepinephrine, in the brain. There is evidence which suggests that the hypotensive action of reserpine may be peripheral rather than central in origin, owing to the depletion of norepinephrine at peripheral nerve endings (16). Consequently, sympathetic nerve impulses cannot influence effector structures because there is no neurohormone available for liberation. The multifaceted aspects of the relationship of serotonin and norepinephrine to reserpine action are the subject of several reviews (5, 17); however, certain relatively recent developments shed an interesting light on this controversial problem. It has been established that the alkaloids deserpidine and rescinnamine, which exhibit both tranquilizing and hypotensive activity, also liberate serotonin and norepinephrine from the brain and deplete norepinephrine at peripheral binding sites. The reserpine analog, syrosingopine (SINGOSERP®), which exhibits primarily hypotensive and bradycardiac actions, releases peripheral norepinephrine but appears to have only a slight influence on the brain amines (5). Tetrabenazine (Ro 1-9569), a synthetic derivative of benzoquinolizine which elicits a

pronounced tranquilizing effect with no significant action on blood pressure (18), releases brain serotonin and norepinephrine but not peripheral norepinephrine. No final conclusion can be drawn at this time as to the relationship between the pharmacologic effects of reserpine analogs and their influence on the tissue levels of specific biogenic amines. The association may possibly be comparable to the relation between the skeletal muscle relaxant action of d-tubocurarine and its coincidental ability to release histamine from tissues.

Although the acute toxicity of reserpine is relatively low, it may cause more annoying untoward reactions than the phenothiazine derivatives, especially in the higher dosage ranges. The side-effects of reserpine which are suggestive of cholinergic stimulation include drowsiness, lethargy, nasal stuffiness, bradycardia, hypotension, increased motor activity of the gastrointestinal tract resulting in diarrhea, and gastric hypersecretion which may lead to exacerbation of peptic ulcer and gastric hemorrhage. Edema, weight gain, altered sexual desire, lactation in nonpregnant women, and increased frequency of seizures in epileptics have been observed. A frequent neurologic manifestation of overdosage is a Parkinson-like syndrome. Nuclear changes have been reported in the neurons of the brainstem, basal ganglia, and cerebral cortex of chronically reserpinized monkeys; however, the cytologic picture was not characteristic of that observed in clinical Parkinsonism (19). Perhaps the most disturbing toxic effect of reserpine is its effect on behavior, which appears to be largely an extension of its therapeutic action. Subjective depression of sufficient severity to necessitate psychiatric treatment or, at times, electroshock therapy is not uncommon. The high incidence and severity of such reactions has prompted the Food and Drug Administration recommendation that the daily dosage of reserpine not exceed 0.25 mg. in non-institutionalized patients. The recent development of reserpine analogs which are highly selective, i.e., which exhibit tranquilizing or hypotensive activity, but not both to a significant degree, may provide drugs of superior clinical utility.

Miscellaneous Ataractic Agents

There are a continually expanding number of drugs of chemically heterogeneous structure which are claimed to possess mild tranquilizing activity and to be of value in the management of psychoneurotic disorders. A few well-designed studies have indicated that

certain members in this group are significantly more effective than placebo therapy in the alleviation of neurotic symptoms. However, many of the claims made for these drugs are substantiated only by inadequately controlled clinical studies. Beecher (20) has reminded us that placebos are astonishingly effective in controlling a great many kinds of unpleasant situations. Furthermore, there is evidence that placebos are more effective when the stress is greater. These remarks are not made to imply that clinical utility is lacking in the mild tranquilizers, but that considerable definitive study remains to establish their use on more than a grossly empiric basis.

One of the most perplexing problems of psychopharmacology is the adequacy of techniques for the experimental evaluation of new molecules, as a basis for the selection of drugs intended for the alleviation of mental disorders. The pharmacologist is charged with the task of detecting compounds of potential value for a variety of clinical syndromes that are poorly defined. The need of valid criteria for differentiation between mild sedative-hypnotic agents and tranquilizers is most acute. It is hoped that progress in neurochemistry, neurophysiology, and related disciplines will provide the basis for a more rational approach to the development of psychotherapeutic agents. The development of drugs which effectively control behavioral disturbances represents an outstanding medical achievement of the past decade; a major goal of the current decade might well be the discovery of compounds which attack the etiologic factors of mental illness.

APPENDIX

Psychotherapeutic Drugs

I. Phenothiazine Derivatives

A. Very Potent

Chlorpromazine [1]	Thorazine ®	(Smith Kline & French)
Fluphenazine [2]	Permitil ®	(White)
	Prolixin ®	(Squibb)
Perphenazine [2]	Trilafon ®	(Schering)
Prochlorperazine [2]	Compazine ®	(Smith Kline & French)
Thiopropazate [2]	Dartal ®	(Searle)
Trifluoperazine	Stelazine ®	(Smith Kline & French)
Triflupromazine	Vesprin ®	(Squibb)

B. Less Potent[3]

Acepromazine	PLEGICIL ℞	(Ayerst)
Mepazine[1]	PACATAL ℞	(Warner-Chilcott)
Methoxypromazine	TENTONE ℞	(Lederle)
Promazine[1]	SPARINE ℞	(Wyeth)
Promethazine[4]	PHENERGAN ℞	(Wyeth)
Thioridazine	MELLARIL ℞	(Sandoz)

C. Phenothiazines With Selective Usefulness

Pipamazine[5]	MORNIDINE ℞	(Searle)
Thioperazine[5]	VONTIL ℞	(Smith Kline & French)
Trimeprazine[1, 6]	TEMARIL ℞	(Smith Kline & French)

II. RAUWOLFIA PREPARATIONS

Rauwolfia[7]	(Rauwolfia, alseroxylon, and reserpine are marketed	
Alseroxylon[7]	under a variety of proprietary names)	
Reserpine		
Deserpidine	HARMONYL ℞	(Abbott)
Rescinnamine	MODERIL ℞	(Pfizer)
Syrosingpine[7]	SINGOSERP ℞	(Ciba)

III. NEUROSEDATIVES OF CHEMICALLY HETEROGENEOUS STRUCTURE

Azacyclonol	FRENQUEL ℞	(Merrell)
Benactyzine	SUAVITIL ℞	(Merck Sharp & Dohme)
Buclizine	SOFTRAN ℞	(Stuart)
	VIBAZINE ℞	(Pfizer)
Captodiamine	SUVREN ℞	(Ayerst)
Ectylurea	NOSTYN ℞	(Ames)
Hydroxyzine	ATARAX ℞	(Roerig)
Piperilate	SYCOTROL ℞	(Reed & Carnick)

IV. NON-BARBITURATE SEDATIVE-HYPNOTICS

Dichloralantipyrine	SOMINAT ℞	(National)
Ethchlorvynol	PLACIDYL ℞	(Abbott)
Ethinamate	VALMID ℞	(Lilly)
Glutethimide	DORIDEN ℞	(Ciba)
Methylparafynol	DORMISON ℞	(Schering)
Methprylon	NOLUDAR ℞	(Hoffman-LaRoche)
Petrichloral	PERICHLOR ℞	(Ives-Cameron)

V. INTERNEURONAL BLOCKING AGENTS WITH NEUROSEDATIVE ACTIVITY

Chlormezanone	TRANCOPAL ℞	(Winthrop)
Meprobamate	EQUANIL ℞	(Wyeth)
	MILTOWN ℞	(Wallace)
Oxanamide	QUIACTIN ℞	(Merrell)
Phenaglycodol	ULTRAN ℞	(Lilly)
Promoxolane	DIMETHYLANE ℞	(National)

VI. Interneuronal Blocking Agents Without Neurosedative Activity [8]

Chlorzoxazone	Paraflex ®	(McNeil)
Carisoprodol	Soma ®	(Wallace)
Diethylpropanediol	Prenderol ®	(Squibb)
Mephenesin	Tolserol ®	(Squibb)
Mephenesin Carbamate	Tolseram ®	(Squibb)
Methocarbamol	Robaxin ®	(Robbins)
Styramate	Sinaxar ®	(Armour)
Zoxazolamine	Flexin ®	(McNeil)

VII. Antidepressives

A. Amphetamines

Amphetamine
Dextroamphetamine
Metamphetamine

B. Anorexigenics (Anorexiants)

Amphetamines (see A)		
Diethylpropion	Tenuate ®	(Merrell)
	Tepanil ®	(National)
Phenmetrazine	Preludin ®	(Geigy)
Phenyl tertiary butylamine resin	Ionamin ®	(Strasenburgh)

C. Amine Oxidase Inhibitors

beta-phenylisopropyl hydrazine	Catron ®	(Lakeside)
Isocarboxazid	Marplan ®	(Hoffman-LaRoche)
Iproniazid	Marsilid ®	(Hoffman-LaRoche)
Phenelzine	Nardil ®	(Warner-Chilcott)
Nialamide	Niamid ®	(Pfizer)

D. Piperidine Derivatives

Methylphenidate	Ritalin ®	(Ciba)
Pipradol	Meratran ®	(Merrell)

E. Other Antidepressant Drugs

Deanol	Deaner ®	(Riker)
Imipramine	Tofranil ®	(Geigy)

[1] Agranulocytosis has been reported in patients treated with these phenothiazines.

[2] Useful in both mild psychoneurotic agitation and in serious psychotic disturbances.

[3] Generally not as effective in control of severe psychotic states, extreme agitation, nausea, and vomiting. May be effective alone in the treatment of milder mental or emotional disturbances.

[4] Widely employed for its antihistaminic activity.

[5] Potent anti-emetic activity.

[6] Almost exclusively used for its antipruritic activity.

[7] Primarily employed for their antihypertensive activity.

[8] Centrally-acting skeletal muscle relaxants claimed to be essentially free from central nervous system depressant activity in the dosages recommended.

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GIBBERELLIC ACID

The Miracle Plant Booster

By Morris Haynes and Gunnar Gjerstad *

NOT since Kogl's discovery in 1934 (1) of the role of indole acetic acid in plant growing has the botanist been so baffled by a class of compounds as he is at present by the gibberellins. Although isolated in the crystalline state as long ago as 1938, these growth regulators did not attract much attention outside of the Orient until 1956. The forbidding nature of the Japanese language, inaccessibility of journals, delayed abstracting, difficulties in the preparation of the gibberellins, and the intervening war all contributed their share to the neglect of the subject. However, since the potentialities of the compounds were pointed out in this country by Dr. J. E. Mitchell (2) and in England by Dr. P. W. Brian (3), it was not long till rapid and substantial progress was being made on all aspects of the problem.

Gibberellin, the generic name of several closely related chemical substances of which gibberellic acid is the best known, exerts marked effects on plant growth and behavior (4). Gibberellic acid is a plant stimulator that promotes the development and division of plant cells. Furthermore, a stimulation of root and bud formation in certain plants has been reported by the same substance. Some gibberellins specifically affect flower development, while others affect plant growth in general.

History

The "Bakanae" disease which literally means "foolish seedling" is caused by a parasitic fungus *Gibberella fujikuroi,* which produces gibberellic acid. The earliest description of this disease is attributed to Konishi, a semiliterate Japanese farmer who dictated an agricultural book in 1809. His observations, not published until 1828, of the disease were based on the "in-yo" philosophy, in which responses are interpreted as resulting from a disturbance of the balance of positive and negative factors (5).

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In the early 1920's, a young graduate of Chiba Horticultural College, Eiichi Kurosawa, came to Taihoku, Formosa to work at the Central Research Institute of the Formosan Department of Agriculture on methods of controlling the Bakanae disease, which at the time was causing severe losses to the rice crop on the island. In the course of his investigation, he drew the following conclusions:

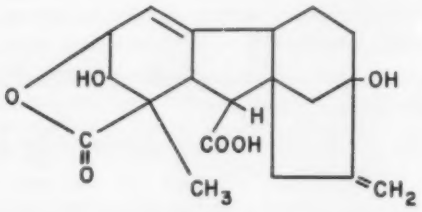
1. The rice "Bakanae" fungus secretes a type of toxin which accelerates rice growth.
2. In addition, the toxin damages root growth and interferes with the formation of chlorophyll.
3. *It is conceivable that the toxin exerts a similar action on other plants besides rice.* (Sic!)
4. The toxin was scarcely altered, even after being kept at 100° C. for four hours.
5. The toxin secreted by the "Bakanae" fungus plays a vital role in differentiating it from similar fungi.
6. It appears that resistivity of the rice plant to the toxin is dependent on the variety.
7. Apparently, the rice plant does not form an antibody against the toxin (6).

During the past thirty years, Konishi's findings have experienced a renaissance by the concerted studies of a large number of Japanese botanists who have been working on a strikingly potent and unusual group of plant growth substances, attracting little attention in the western world. They were named gibberellins after the fungus by a group at the University of Tokyo, notably by Yabuta, Sumiki, and Hayashi, who are credited with the isolation of gibberellic acid and the study of its properties (7).

About five years ago, their work came to the attention, apparently independently, of a group at Imperial Chemical Industries in Great Britain and another group at the United States Department of Agriculture. These two confirmed the Japanese work and contributed their own findings (5). To date, over 800 publications on this topic have appeared and the list of contributions is increasing, so to speak, daily.

Chemistry

Gibberellic acid is a tetracyclic dihydroxylactonic acid, with a chemical formula of $C_{19}H_{22}O_6$. Although its chemical structure has not definitely been proved by synthesis as of now, its agreed structure is:



Gibberellic Acid

As will be seen, gibberellic acid has 8 asymmetric carbon atoms; hence, has 256 optical isomers, and cis-trans isomerism. Its structure is rather complex, being an unstable tetracyclic unsaturated lactone, a type of compound which is rather rare in biological systems. So far, gibberellic acid has not been synthesized, and its successful systhesis seems rather remote due to its complex stereochemistry. Even if it could be produced *in vitro*, it is highly doubtful if its price could compete with that of the biological product.

The present method of manufacture is by submerged synthetic cultures of *Gibberella fujikuroi*. The yield is relatively low, 10 mg. per liter of medium. In addition, several other related entities are formed.

General Physical Properties

Gibberellic acid, in pure form, is a white crystalline powder. Its molecular formula is $C_{19}H_{22}O_6$, and it has a molecular weight of 364.4. The melting point of this compound is 242°C., and its specific rotation is +75.2°.

Solubility

The "miracle booster" has a water solubility of 6 mg. per ml. at 25°C. It is readily soluble in cold methanol, ethanol, isopropyl alcohol,

and acetone. It is less readily soluble in ether, ethyl acetate, and petroleum ether.

In 1956, the wholesale price of pure gibberellic acid was forty dollars per gram. Commercial processes for producing this scarce substance were soon discovered and, in 1957, a gram of gibberellic acid cost ten dollars. At the present, the price for the same quantity is two dollars. The trend in the price of gibberellic acid will probably follow the same pattern in the future, at least for a while. Cost should present no problem to its commercial use since it is applied in micro quantities (10 ppm.).

Application

There are a variety of ways in which gibberellic acid can be administered to plants. If one point of a plant is sprayed, the entire plant is affected. The most effective and efficient method of applying the chemical is to the growing plant in an aqueous solution as a foliar spray, although other plant parts absorb the stimulus as well. Nutrient solutions may not prove economical because the chemical may be destroyed by soil microorganisms.

Gibberellic acid is absorbed through the epidermis of stems or leaves, on both young and mature plant parts, from either alcoholic or aqueous solutions, or from lanolin pastes. Germinating seeds are usually treated with dusting powders which are admixtures of talc or other inert carriers (8).

General Effects of Gibberellic Acid on Growing Plants

1. Almost all flowering plants are affected by or respond to gibberellin treatment, particularly gibberellic acid.
2. A given species or variety responds to a wide range of concentrations, and different species and varieties within a species react differently to the same treatment. Young plants are usually more sensitive than old ones but, as with most environmental stimuli, a certain size has to be attained before flowering can be accelerated.
3. Some effects on herbaceous plants are noticeable within hours, while a discernible response on woody plants may take several days or weeks.

4. Gibberellin is highly mobile and its distribution is systemic in most herbaceous plants but not necessarily in woody plants or those with large storage tissues. Responses are often induced at points considerably removed from the site of application; accordingly, complete coverage in foliage applications may not be essential.
5. The stimulatory effects are temporary; thus, for continuing response, repeated doses are required.
6. Both cell elongation and normal cell division are promoted. These properties are not unique, however, with gibberellin since they also are given in many naturally occurring substances extractable from plants and have a number of similar effects as those of the synthetic auxins and kinins.
7. The primary stimulus is on growth of plant parts above ground. Leaf areas and length of the main stem axis are increased. Upright plants grow taller, and creeping plants become more upright. Root growth and enlargement may be significantly altered under certain conditions.
8. New growth is often paler green or chlorotic. This may be partially offset by maintaining high fertility levels, particularly of nitrogen.

Other favorable effects produced by gibberellic acid are that the amount of total soluble carbohydrates, particularly the glucose fraction, is increased in young wheat and pea plants supplied with gibberellic acid in the nutrient solution. Also, gibberellic acid reportedly may substitute for the red light requirement for germination of certain seeds.

Toxicity

If gibberellic acid is to be used in agriculture on a large scale for the production of food and forage crops, an absolute prerequisite is that it is totally nontoxic to human beings and livestock. A recent study which was carried out in the laboratories of Merck and Co. showed that oral doses of gibberellic acid of 25 grams per kilogram failed to cause death or to produce more than minor signs of toxicity in mice. Studies on chronic toxicity are, at present, not available due

to the recent discovery of gibberellic acid. The LD_{50} for mice is 6.3 grams per kilogram. Since this is so, we can safely conclude that the application of gibberellic acid to food crops as well as to biological drug plants will not lead to untoward side effects since gibberellic acid is used in so small concentrations that, by chemical means, it is very difficult to ascertain its presence in treated plants. The order of acute and subacute toxicity of gibberellic acid is such that it is relatively harmless when administered orally, parentally, by inhalation, or by topical application (9).

Available Products

The miracle plant booster has been put into preparations in different ways. One company has marketed four different types of formulations. One mixture is called Gibrel "88" Seed Stimulant. This preparation, especially designed for seed treatment, is a powder containing 0.88% of potassium gibberellate. Gibrel Emulsifiable Concentrate, another formulation, is intended for use in foliar sprays and contains approximately 4 Gm. potassium gibberellate per quart. The Concentrate contains inert solvents, surfactants, and expanders. It is miscible with water and will not settle out in the spray tank, ensuring full and uniform treatment. It may also be used in aircraft- and low-pressure ground-spraying equipment (10). Gibrel Concentrate for Aerosol Formulations contains 0.05% w/w potassium gibberellate per gallon. A quantity of 12-oz. of this preparation is adequate for treating about 150 five-inch plants. One gallon of the Concentrate is sufficient to prepare approximately 85 twelve-ounce aerosol cans. In addition to the special formulations described above, Merck also produces Gibrel in bulk, one mixture containing 0.5% potassium gibberellate (Mixture Type B), another containing 10% potassium gibberellate (Mixture "10%") (10). Gibrel is the brand name for the plant growth substance.

When dissolved in anhydrous ethanol, isopropyl alcohol, or other suitable anhydrous solvents, Gibrel is stable for a very long time. Gibrel, however, is not stable in aqueous media and should only be diluted with water at the time the spray is to be applied. Any remaining aqueous spray should not be stored for future use since Gibrel will rapidly lose potency (10). It is especially sensitive to warm acids or alkalis.

Potential Uses

Scientists at the Agriculture Research Center in Beltsville, Maryland, have doubled and, in some instances, tripled the height of many kinds of plants by one treatment or other with the new chemical (11).

Horticulture Plants

In greenhouse experiments, they applied gibberellic acid in a lanolin paste to the young stems of geraniums, poinsettias, roses, dwarf dahlias, petunias, and asters. In from three to four weeks, the treated plants were three times as tall as untreated ones. In all cases, gibberellic acid caused the treated plants to grow much taller, flower up to one month earlier, and develop seeds much sooner than control plants. The treated plants require lower temperature and less illumination than the controls for full development. These findings offer great promise for the floricultural science.

Field Crops

In the field, the height of crop plants—such as soybeans, snapbeans, corn, barley—in many cases was doubled and in some cases tripled, and the weight and solid matter in young snapbeans was increased by thirty to forty per cent during the first two or three weeks following treatment with gibberellic acid.

The treatment of barley seeds with gibberellic acid produces stimulation of germination and a higher amylase production. The stimulus aids in producing a successful stand of grain during adverse weather conditions.

Treated corn is aided in overcoming the effects of summer drought, even without very striking growth responses. "Some work has shown that corn roots, as well as top growth, may be stimulated during the first weeks of growth" (11).

Seed treatment with gibberellic acid permits growers to plant cotton early enough to benefit from good weather throughout the growing season, thus avoid many of the risks of poor germination, slow growth, or seedling standstill which otherwise may necessitate replanting.

Treating soybean seeds with gibberellic acid speeds emergence and results in a longer stem. The faster emergence allows farmers to begin weed control early, and the longer stem should result in higher yields because of less loss during harvesting. An increase in

height might save many more beans from the lower part of the plant that are otherwise often lost in combining. Some experiments have shown that, in harvested bean fields, as much as two bushels of beans and two bushels of uncombined pods were left scattered on the ground or on the stubble of plants. Saving the beans from one more pod per plant would add up to two bushels or more per acre.

For fall-planted wheat, such is the case in Texas, faster and more complete emergence would promote the growth to withstand freezing winters. A thicker stand usually indicates an increase in yield. Treatment with gibberellic acid appears to increase the rate of emergence during cold, wet weather.

The application of gibberellic acid to Kentucky Bluegrass speeds up the growth in the spring. This added growth will possibly help it to overcome the punishment of the hot, dry summer weather. The yield of dry matter and nutritional value is increased by 33 per cent.

Vegetables

Gibberellic acid can be applied to carrots to produce seed in a very short time. The treated plants can produce seed the first year, bypassing normal vernalization.

When treated with 100 micrograms of gibberellic acid weekly for eight weeks, some cabbage plants grow to be fifteen feet tall. This is a disadvantage to head cabbage because only a stalk is formed, although it is an advantage toward producing seed.

Treated celery showed growth responses within five days, and these responses usually reached a maximum within three weeks. After treatment, some undesirable effects occurred. The treated celery became lighter green; wilting was more prevalent in hot, dry weather; and plants were susceptible to diseases. However, by the use of good agriculture practices, gibberellic acid properly applied may be an important factor in speeding up maturity of early celery in the northern states and for increasing yields and reducing time to marketable maturity throughout the season.

Gibberellin-treated radish may be significant in the production of seed crops. In several experiments, a single foliar spray of 1,000 ppm. (parts per million) of gibberellic acid promoted earlier and more uniform seedstalk development, flowering, and seedpot maturity.

Gibberellic acid can be sprayed on lettuce when it is at the 8-10 leaf stage. The seedstalk will form early with a high yield. This is

advantageous for producing seed, but not for lettuce heads because a seedstalk will form instead of a head.

Fruits

A great increase in berry set and size and a promotion of the formation of looser clusters can be obtained from grapes sprayed with gibberellic acid at bloom or shortly thereafter. Seedless grapes sprayed with gibberellin have exceeded all expectations in that excellent sets of berries have been achieved, and there has been no loss of quality. The practical advantages envisaged for the use of gibberellin on seedless grapes include the increased tonnage per acre resulting from increased set and size of clusters and berries, appreciable savings in girdling and cluster-thinning expenses, and looser clusters facilitating better pest-control, making possible a higher quality fruit.

Significant increases in fruit set of oranges have resulted from spraying the flowers or small fruits with gibberellic acid. These increases resulted with no loss in final fruit size, nutritional or edible quality or color. Treated navel oranges produced a slightly better color, thinner rinds, and a higher percentage of abortive seeds. Gibberellin applied to nearly mature navel oranges reduced rind thickness and coloration and increased juice content and the vitamin C concentration in the juice (12).

Tomatoes treated with gibberellic acid can form fruit without pollination. This fruit will have no seeds and will ripen uniformly.

Drug Plants

The problem if gibberellic acid will influence the biosynthesis of secondary plant metabolites of interest to the healing arts; *i.e.*, glycosides, alkaloids, antibiotics, has not been studied to any appreciable extent to date. One publication which has appeared in recent literature indicates strongly that the gibberellins may not be favorable for the biogenesis of the digitaloids (13). More work along these lines is in progress in the authors' institution.

Mode of Action

The demonstrable effects of gibberelliic acid resemble those of indole acetic acid with regard to stem extension, parthenocarpic fruit development, cambial activity, and leaf abscission. In these instances, these chemicals appear to act synergistically. However, as regards

root initiation and development of lateral buds, their actions are antagonistic. This fact defeats the theory that gibberellic acid acts as an inhibitor of indole acetic acid oxidase. Such an auxin-sparing effect cannot explain all manifestations of gibberellic acid activity (14).

In conclusion, it can be stated that gibberellic acid has for many plant responses served as a major scientific breakthrough for the horticulturists, agronomists, plant physiologists, and perhaps even the plant pathologists. Only with this consideration in mind can one evaluate gibberellic acid in terms of its future potentialities in crop production. It offers a way of controlling important responses heretofore, at least on intact plants, not easily subject to chemical regulation. These responses include elimination of dwarfism, reversal of virus stunting, elongation of stems, expansion of leaves, increased production of dry matter, acceleration of flowering in biennials and long-day annuals, promotion of uniformity in growth, flowering, and fruiting, increased flower size, control of fruit size and maturity, reduction or replacement of cold and photoperiodic requirements for growth and flowering, and promotion of normal growth rates at suboptimal temperatures.

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SELECTED ABSTRACTS

Bioflavonoid Therapy of Rh Immunized, Pregnant Women. Jacobs, W. M. *Surgery, Gynecol. and Obstet. 110:*33 (1960). Interest in bioflavonoid compounds and their action in preventing or reducing capillary fragility was recently directed toward the application of this activity in preventing or reducing iso-immunization of Rh negative mothers during pregnancy. It has been fairly well established that Rh iso-immunization occurs through the entrance of Rh positive fetal cells into the maternal circulation by means of breaks in the placental capillary system. Such breaks do occur but, if these breaks could be reduced or eliminated by decreasing capillary fragility, the degree of iso-immunization might be minimized. Rh antibodies are known to be small and freely cross the placental barrier; therefore, antibodies already present would not be affected but, if further transfer of fetal cells could be prevented, the antibody titer could be held from further rise. The likelihood of infant survival would, thus, increase.

On the premise that bioflavonoid compounds might act to reduce these breaks in the placental capillary system, 400 to 600 mg. a day of bioflavonoids (CVP capsules) were given, from the early part of pregnancy until delivery, to a group of 32 Rh negative mothers immunized by either previous pregnancies or by blood transfusion with Rh positive blood. A group of 71 similar Rh negative mothers were not given bioflavonoids but were treated the same otherwise, including preterm delivery, if feasible, and early exchange transfusion to the newborn infant. In the bioflavonoid treated group, there were 3 stillborn infants, 5 that died in the immediate neonatal period, and 24 that survived after one or more exchange transfusions. The survival rate was thus 75 per cent. In the non-treated group of 71 mothers, there were 23 stillborn infants, 26 that died in the immediate neonatal period, and 22 that survived after one or more exchange transfusions. The survival rate in the non-treated group was 30.9 per cent.

The author stated that, although the results appear to be very striking in favor of the use of bioflavonoids to reduce the severity of erythroblastosis fetalis, further studies should be undertaken with more patients in order to substantiate these results.

Dimethisterone, A New Orally Active Progestational Agent. David, A., Fellowes, K. P., and Millson, D. R. *J. Pharm. Pharmacol. 11:*491 (1959). The authors reported studies of some of the biological properties of dimethisterone, 6α:21-dimethylethisterone, an orally active progestational drug recently developed. Dimethisterone is a tasteless, white, crystalline compound which is almost insoluble in water but soluble in alcohol.

Animal studies were planned to evaluate the acute oral toxicity, the progestational activity, anabolic and androgenic activity, estrogenic activity, and the effect of dimethisterone on salt and water balance.

The acute oral LD_{50} in mice was found to be 7.65 Gm./Kg., thus indicating that dimethisterone is a relatively non-toxic drug. The hormone was found to have significant progestational activity in a comparative study with ethisterone in rabbits. Dimethisterone was found to have an oral progestational activity 11½ times that of ethisterone. On the other hand, in ovariectomised mice, dimethisterone showed no estrogenic activity up to a total dose of 32 mcg./20 Gm., with estrone used for control purposes.

The anabolic and androgenic activity of the new hormone was evaluated in castrated rats, using testosterone propionate as the reference compound. Up to a dose of 64 mg./Kg. per day (a series of 7 daily injections were given), there was no evidence of anabolic or androgenic activity by dimethisterone. In rats, there was also found to be no sodium or potassium retention during the 24 hours after oral administration of the new hormone, although there was a slight diuretic effect with the top dose of 32 mg./Kg.

The authors concluded that dimethisterone would appear to hold promise as a therapeutic agent where oral progestational activity is indicated.

The Evaluation of Antibiotic Activity in Sera Following Administration of Three Penicillins. Griffiths, R. S. *Antibiot. Med. and Clin. Therapy 7:*129 (1960). Healthy, fasting adults were given single 250 mg. doses of potassium penicillin V, potassium penicillin G, and alpha-phenoxyethyl penicillin. Blood samples were withdrawn at prescribed intervals up to six hours following ingestion of the antibiotic. The serum was separated and divided into two, one being tested by the serial dilution tube technique against beta-hemolytic

Streptococcus C203 and the other against *Staphylococcus aureus* 209P. The one-half or one-hour blood sample showed the greatest antibacterial activity in most cases.

It was found that potassium penicillin V gave approximately three times the activity against the Streptococcus and 5 times the activity against the Staphylococcus as compared with potassium penicillin G. When potassium penicillin V was compared with alpha-phenoxyethyl penicillin, the antibacterial activity of the former was almost half again higher than that of the latter.

In commenting on the tube dilution technique, the author stated that this method of evaluation of antibiotics is much superior to that of designating serum concentration levels achieved. A new antibiotic might be better absorbed and thus attain a higher concentration in the blood serum than other comparable antibiotics, but its activity against certain pathogenic microorganisms might be lower. Or, the new antibiotic might require a higher concentration than another to effectively kill pathogenic microorganisms. Therefore, its antibacterial activity in the blood stream is of greater significance in evaluating the probable clinical effectiveness of the new antibiotic. The author emphasized that, before a new form of an antibiotic is assumed to be better than another, the antibacterial activity of both in the sera must be compared against representative pathogenic bacteria.

A New Orally Active Diuretic Agent, Disamide. David, A., and Fellowes, K. P. *J. Pharm. Pharmacol. 12*:65 (1960). Some of the pharmacological properties of 5-chloro-2,4-disulphamyltoluene (Disamide) were reported by the authors. This new oral diuretic agent was tested in mice and rats and was shown to be more than twice as active as chlorothiazide and approximately equal in activity to acetazolamide as a diuretic agent.

The mechanism by which Disamide produced diuresis appeared to be a dual mechanism, having some of the characteristics of acetazolamide and of chlorothiazide. Acetazolamide exerts its diuretic effect largely by inhibiting the carbonic anhydrase of the cells of the renal tubules. This prevents the re-absorption of bicarbonate followed by an osmotic diuresis with a high urinary bicarbonate content. Disamide exhibited about 40 per cent of the carbonic anhydrase inhibiting

activity as compared with acetazolamide. Chlorothiazide exhibits little carbonic anhydrase inhibitory activity but exhibits a high chloride excretion with approximately an equimolar sodium excretion. When compared with chlorothiazide, Disamide was found to cause a greater diuresis with one-half the dose. One-half the dose also caused about the same sodium and chloride excretion as chlorothiazide.

Further evidence that Disamide had a dual mechanism of action was given by the authors in that Disamide did not show a diminution of diuretic activity over a prolonged period of administration. Had carbonic anhydrase inhibition been its primary mechanism of action, it would have been expected that there would have been a diminution of activity such as is the case with acetazolamide.

Disamide was also found to have a low acute and chronic oral toxicity in tests on mice and rats. It had no effect on blood pressure or respiration and no analgesic, hypoglycemic, or antibacterial properties. Its anticonvulsant properties were similar to those of acetazolamide.

Water Absorption by Petrolatum Ointment Bases. Groves, G. A., and de Boucier, D. J. G. *Canadian Pharm. J. 93:37* (1960). The authors attempted to increase the water absorbing capacity of petrolatum as an ointment base by the addition of a series of Spans and Tweens. Initially, it was found that 20 Gm. of petrolatum absorbed 1.2 ml. of water, corresponding to a water number of 6.0.

Five per cent of Span 20, 40, 60, and 80 and Tween 40, 60, and 80 were incorporated separately in petrolatum. Twenty grams of each of these mixtures were triturated with water until no more water was taken up. The base was then chilled for an hour in an ice bath, warmed to room temperature, and then levigated on a slab. If water was exuded, the process was repeated using 0.1 ml. less water. The bases were also tested for stability by placing them in a constant humidity chamber (47.2 per cent relative humidity) and in an oven at 37° C. Thus stored, they were evaluated on the basis of "sweating."

The authors found that the Spans increased the water absorption properties of petrolatum more than did the Tweens, although there was an increase in all cases as compared with petrolatum alone. The preparations, when saturated, resulted in smooth, soft, white creams of the water-in-oil emulsion type. Span 80 increased water absorption

to 33 ml., several times more than any other Span. Further studies with Span 80 showed that a maximum absorption of 48 ml. (water number 240) occurred with a concentration of 1.5 per cent of Span 80. Concentrations of 2.5 per cent or above resulted in a constant absorption of about 33 ml. of water.

Carbowax 1540 was also incorporated with petrolatum in concentrations ranging from 5 to 50 per cent. It was found that Carbowax 1540 provided only a slight increase in the water absorbing properties of petrolatum. However, by the addition of Span 80 to the Carbowax-petrolatum mixtures, a marked increase in water absorption was noted. In a concentration of 2 per cent, Span 80 increased the water absorption of a 25 per cent Carbowax 1540 in petrolatum to 58 ml. and a 50 per cent mixture to 38 ml. When the Span 80 concentration was increased to 10 per cent, these two mixtures absorbed 136 ml. and 86 ml. of water, respectively.

The authors concluded that the optimum concentration of Span 80 in petrolatum for increasing its water absorbency is 1.5 per cent. An ointment base of suitable viscosity was obtained. It showed satisfactory stability as indicated by the amount of "sweating". In the presence of Carbowax 1540, a much higher concentration of Span 80 (10 per cent) was found to be optimum for increasing water absorbency. The authors concluded that this could be explained on the basis of an initial formation of a water-in-oil emulsion followed by phase reversal to a stable, water-washable, oil-in-water emulsion.

A Comparative Study of Erythromycin Salts and Triacetyloleandomycin. Quinn, E. L., Colville, J. M., and Cox, F., Jr. *Antibiot. Med. and Clin. Therapy 7:*103 (1960). A comparative study was undertaken in which erythromycin propionate was evaluated in certain respects in relation to erythromycin stearate and triacetyloleandomycin. A group of 10 healthy young men were given a single fasting dose of 500 and 1000 mg. of erythromycin propionate and another group of 10 healthy young men were given five 500 mg. doses of erythromycin propionate at six-hourly intervals. Both groups had previously participated in like studies with erythromycin stearate and triacetyloleandomycin.

Triacetyloleandomycin was found to produce serum concentrations following single or multiple doses that were higher than those

produced by erythromycin propionate or erythromycin stearate. At three and six hours following oral ingestion of the antibiotics, the serum concentration was about 3 to 5 times higher after triacetyloleandomycin than after erythromycin stearate but less than 2 times higher than after erythromycin propionate. However, it was noted that two hours after the fifth six-hourly dose (26 hours after the initial dose) of the antibiotics, the serum concentration of erythromycin propionate was considerably higher than it had been after the first dose and considerably higher than the triacetyloleandomycin concentration. Such an increase was not found following the same dosage schedule of triacetyloleandomycin and of erythromycin stearate.

An evaluation of the serum antibacterial activity showed a different relationship than did the serum concentrations. The antibacterial activity of the serum was 10 to 20 times higher after erythromycin propionate and 2 to 14 times higher after erythromycin stearate than after triacetyloleandomycin. It was also found that the antibacterial activity of the serum two hours following the fifth six-hourly dose of erythromycin propionate was about twice as high as that obtained after the first dose. Along with the higher serum concentration, this finding would indicate that there is apparently some degree of accumulation in the serum of erythromycin propionate following multiple doses. This did not occur with the other two antibiotics. The antibacterial activity of the urine was also found to be greater following erythromycin propionate.

The authors pointed out that measurements of the antibacterial activity of the serum and urine provide more useful clinical information than serum concentrations. The former reflects more accurately the antibiotic's antibacterial potency in therapy.

The Clinical Use of Epoxypropidine in Neoplastic Disease. Miller, D. G., Diamond, H. D., and Craver, L. F. *Clin. Pharmacol. and Therapeut. 1*:31 (1960). In the evaluation of a series of bis-epoxide alkylating agents, epoxypropidine (1,1′-bis(2,3 epoxypropyl)-4,4′-dipiperidyl) was found to be the most active antileukemic agent and was found to possess the physical characteristics desirable for a pharmacologic agent. Clinical evaluation of this compound was un-

dertaken in 21 patients having neoplastic diseases not amenable to surgery.

A dose of 5 mg. per Kg. of body weight was found to induce leukopenia and thrombocytopenia to the degree and of the duration ordinarily seen with 0.4 mg. per Kg. of nitrogen mustard. Smaller doses, 2 to 3 mg. per Kg., were used in patients whose marrow function was compromised for any reason.

Although epoxypropidine was found to be more active by weight than diepoxypropylpiperazine (another epoxide alkylating agent with which the authors had had clinical experience), there was no evident therapeutic advantage in the patients of this series. However, some of the side effects were considerably milder than those with diepoxypropylpiperazine or nitrogen mustard. Nausea and vomiting occurred with doses of 2 to 3 mg. per Kg. of body weight or more, but these symptoms were mild and usually subsided in 24 hours without the use of sedatives or antiemetics. There were no instances of visual aberrations as had occurred with diepoxypropylpiperazine. This diminution of side effects made it unnecessary to hospitalize patients undergoing therapy, in contrast to therapy with other antineoplastic agents.

Certain implications of these findings were expressed by the authors. Epoxypropidine fulfilled the requirements for biologic activity, stability of configuration, and solubility. Its increased basicity made it approximately ten times more active on a weight basis than diepoxypropylpiperazine. However, its therapeutic index and its range of activity appeared to be no greater than those of its piperazine analogue. The effect on malignant cells of all of the clinically useful alkylating agents is limited by the concomitant effect on the bone marrow, and all of them share virtually the same spectrum of activity. It was, therefore, concluded that findings to date would argue against the probability of increasing anticancer activity of the alkylating agents by altering prosthetic groups.

BOOK REVIEWS

Unpublished Abstracts of Articles on Pharmaceutical Subjects, Series 8, Compiled by Henry M. Burlage, Dean and Professor of Pharmacy and Pharmaceutical Chemistry, College of Pharmacy, The University of Texas.

This is the eighth of a series of unpublished abstracts covering various pharmaceutical subjects all of which are available at a nominal cost by writing to the compiler. Copies of Series 1, 2, 3, and 4 are available at one dollar each; Series 5 and 7 are available at a dollar and a half; and Series 6—and, this, the most recent, Series 8—at two dollars each. Series 8 also contains a cumulative subject and title index covering all of the Series, 1 through 8, as well as a cumulative index of authors. Teachers and research workers will find these unpublished abstracts of considerable interest and value and it is a service which is well worth the nominal charge to cover printing and mailing costs.

L. F. TICE

Vitamin A. Thomas Moore. xx + 645 pp. Elsevier Publishing Company, New York City 28, N. Y., 1957.

The author, an active researcher in the field of vitamin A, has compiled into this work a summary of the literature published dealing with the vitamin. Not only has he presented data on vitamin A obtained by nutritionists and biochemists, but he has brought together material covering all the cognate sciences, including chemistry, physics, physiology, pathology, medicine, agriculture, and natural history. Special attention is given to relationships existing between vitamin A and sex hormones.

The text is divided into eight parts comprising a total of 39 chapters. An appendix and a detailed index are at the end of the book.

Part I deals with the historical introduction of vitamin A; Part II covers the quantitative determination of vitamin A and its provitamins; the chemistry of vitamin A and its provitamins and congeners are discussed in Part III; Part IV reviews the comparative biochemistry and natural history of the carotenoids and vitamin A; in Part V are discussed the physiology and biochemistry of vitamin A and its provitamins and congeners; in Part VI is reviewed the pathology of vitamin A deficiency or excess; Part VII deals with vitamin A in the human; and a group of special topics are discussed in Part VIII.

This text has been prepared in a very thorough and scholarly manner. It should be beneficial as a reference work in college courses in nutrition, dietics, biochemistry, organic chemistry, pharmacy, medicine, physiology, and agriculture.

MARTIN BARR

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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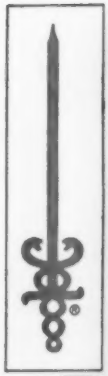

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